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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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LICATLA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053

EXAMINER

SCHULTZ, JAMES

ART UNIT PAPER NUMBER

1635

DATE MAILED: 01/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No. 09/913,800	Applicant(s) MONIA ET AL.	
Examiner J. D. Schultz, Ph.D.	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 05 November 2004.
- 2a) This action is FINAL.
- 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1,2 and 5-18 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1,2 and 5-18 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 8/16/2001.
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____

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DETAILED ACTION

Election/Restrictions

Applicants' election with traverse of Group I in the reply filed on November 5, 2004 is acknowledged. The traversal is on the ground(s) that the prior art cited does not teach the special technical feature of applicants' instant claims, and that therefore, the Groups do not lack unity. Specifically applicants point out that the oligo of Draper constitutes only a 7 nucleobase portion of SEQ ID NO: 21, while the limitations of the instant claim 1 require that the oligo be at least 8 nucleobases of SEQ ID NO: 21. This is not adopted, because the oligo of Draper shares homology over 10 nucleobases. However, because it is not considered a burden to search the claims of Groups I and II together, Groups I and II are hereby rejoined and fully examined herein.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on August 16, 2001 was filed before the mailing date of the first Official action on the merits enclosed herewith. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner, and a signed copy is attached.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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1. Claims 15-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of Akt-2 expression *in vitro*, does not reasonably provide enablement for antisense-mediated inhibition of Akt-2 expression *in vivo*, or for methods of treating diseases associated with its expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The above invention is drawn to methods of using an 8 nucleobase portion of SEQ ID NOS: 32 or 21 in inhibiting the expression of Akt-2 in cells or tissues, or to methods of treating an animal having a condition associated with Akt-2, comprising contacting said cells or tissues with antisense compositions that inhibit the expression of Akt-2. The language of said claims either encompasses or expressly claims *in vivo* activity.

The specification teaches prophetic methods of treatment using antisense oligos targeted to Akt-2, with broad treatment regimens that include pharmaceutical formulations, and treatment regimens comprising, for example, antisense administration at concentrations between 0.01 μg to 100 g per kg of body weight, from once or more daily, weekly, monthly, or yearly, or even once every 2 to 20 years. The specification provides exemplification only for methods of using the claimed compositions to inhibit the expression of Akt-2 in cultured cells *in vitro*.

The specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of an antisense compound *in vivo* based solely on its performance *in*

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vitro is difficult at best. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of antisense treatment.

A recent (2002) review article by Braasch et al. concludes that major obstacles persist in the art of using antisense oligos in treating disease: “gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable” (Pg. 4503, para. 1 and 2). Braasch et al. specifically identify 3 factors that contribute to the unpredictable efficacy of using antisense compounds in general: 1) the variable capability of antisense oligonucleotides to access sites within the mRNA to be targeted; 2) problems pertaining to the delivery and uptake of the antisense oligos by cells, with the result that “the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death”; and 3), that “oligonucleotides can bind to

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proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. elaborates, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target, and that "[a]ttempts to describe the *in vivo* structure of RNA, in contrast to DNA, have been fraught with difficulty." (Page 3161, second column).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states that "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for

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in vivo situations.” (Page 379). Gewirtz adds that [t]he other major problem in this field is the ability to deliver ODN (oligodeoxynucleotides) into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient.”

Branch et al. discuss the problems pertaining to non-specific oligo interactions that lead to artifactual phenotypes during *in vivo* antisense administration: “non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis” (Page 50), while Tamm et al. states that “[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally” (page 493, right column).

Further, regarding the therapeutic benefit of antisense technology in general, Branch states that “in fact, nucleic acid drugs should not be thought of as magic bullets. Their therapeutic use will require vigilant monitoring. Compared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs extend only across a narrow concentration range. Both *in vitro* and *in vivo*, less than a factor of ten often separates the concentration producing no antisense effect from that producing the full antisense effect. Steep dose-response curves commonly indicate that a drug has multiple, synergistic mechanisms of action. A drug with a narrow therapeutic window can be potent and extremely valuable, but can also be tricky to use safely. Since the ratio of antisense to non-antisense effects drops sharply outside a restricted concentration range, it will be challenging to obtain consistent therapeutic benefit (Page 46, second column).

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Tamm et al. concludes by stating that until “the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach.”

Finally, Branch states that “[i]t is not yet clear whether *in vitro* screening techniques of the sort used by Milner and co-workers will identify ODNs that are effective *in vivo*. With so many possible sequences to choose from, and the likelihood that *in vitro* studies will not always predict *in vivo* efficacy, straightforward new screening techniques need to be developed for use in cells.”

Thus, it is maintained that the prior art at the time of applicants’ filing would not enable the use of *in vitro* antisense screening techniques to support claims directed to the *in vivo* use of antisense, let alone claims directed to therapeutic use *in vivo*. Accordingly, one skilled in the art, being unable to use the prior art for such guidance, must necessarily find such guidance from the specification. However, one of skill would not find the guidance provided in the specification in the form of *in vitro* examples and broad prophetic treatment regimens enough to overcome the art recognized unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references above.

This is particularly true in view of the breadth of claim 16, which is drawn to treating or preventing any condition or disease suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment

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effects provided by the antisense administered, and specifically regarding the instant compositions and methods claimed.

Since the specification fails to provide any real guidance for the methods of using antisense *in vivo* or in the successful treatment or prevention of such a broad range of diseases, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of those sequences that are successfully delivered to target sites in appropriate cells and /or tissues such that inhibition is achieved and treatment attained. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002

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do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 2, 12, and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Hardin et al. (U. S. Patent Number 6,083,695).

The claims of the above invention are drawn to antisense compounds 8 to 30 nucleotides in length that comprise an 8 nucleobase portion of either of SEQ ID NOS: 32 or 21, and to such compositions in pharmaceutically acceptable diluents.

Hardin et al. teach a sequence (SEQ ID NO: 100) that possesses 100% identity to nucleobases 2 through 9 of SEQ ID NO: 21 of the instant application, which is thus an 8 nucleobase portion of SEQ ID NO: 21. Hardin teaches that this nucleotide oligo is a primer that is used in PCR, and is used in solutions suitable for administration to cellular and molecular biological matter, which is considered to be appropriate as a pharmaceutical diluent. Hardin is thus considered to teach all the limitations of the above claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

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provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 5-11, and 15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-19 of U.S. Patent No. 6,043,090. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims specifically claim SEQ ID NOS: 32 and 21 as instantly recited, and because the instant dependant claims 2 and 5-11, which are drawn to oligonucleotide modifications, are identical to modifications of the patented claims.

The instant claims are drawn to an 8 nucleobase portion of SEQ ID NOS: 32 or 21, and to specific backbone, sugar, nucleobase, and chimeric modifications and methods of use thereof.

Claims 1, 2, 5-11, and 15 of U. S. Patent Number 6,043,090 are drawn to antisense oligos up to 30 nucleotides long that include SEQ ID NOS: 32 and 21. The patented claims are also drawn to the identical backbone, sugar, nucleobase, and chimeric modifications and methods of use thereof as instantly claimed.

Conclusion

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

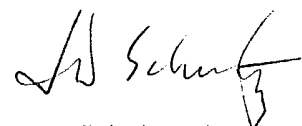
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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JD Schultz, PhD



JD Schultz, PhD
Patent Examiner
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